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| EXAMINER | |
|---|---|
| CANELLA, KAREN A | |
| ART UNIT | PAPER NUMBER |
| 1642 | |

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/936,266 | GLOCKNER ET AL. | |
| | Examiner | Art Unit | |
| | Karen A Canella | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☐ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *1-24 and 44-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *25-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/12/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Acknowledgement is made of applicants election with traverse of Group II, drawn to a device for the in vitro testing of active substances in cells. The traversal is on the grounds that the art cited by the examiner to demonstrate that the instant invention lacks Unity of Invention was improper because the art was not applied after amendment of the parent PCT application. This has been considered but not found persuasive. The instant claims are obvious over the art as evidenced by the rejections set forth below. Thus, the instant invention does not have a special technical feature which would impart Unity of Invention to the instant claims and restriction for examination purposes is proper.

Claims 1-45 have been amended. Claim 46 has been added. It is noted that the preliminary amendment was not properly entered at the time the restriction requirement was made. Accordingly, Group I, drawn to methods for the in vitro testing of active substances in cells, encompasses amended claims 1-24 and 44-46; elected Group II, drawn to a device for the in vitro testing of active substances in cells, encompasses amended claims 25-43. Claims 1-24 and 44-46, drawn to a non-elected invention, is withdrawn from consideration. Claims 25-43 are examined on the merits.

### *Claim Objections*

Claim 30 is objected to because of the following informalities: Claim 30 recites "wherein cell culture container" rather than "wherein the cell culture container".. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claim 25 recites "a cell culture container suitable for collecting a cell culture". It is unclear what the term "collecting" encompasses as it can be read as containing a cell culture, expanding cultured cells, harvesting cultured cells, etc. Further, the metes and bounds of the term "suitable" cannot be determined as this would appear to be a relative term without a definition supplied by the specification.

(B) Claim 25 recites "adjusted active substance concentration-time curve". The metes and bounds of what constitutes said adjusted concentration-time curve cannot be determined. As stated it would read on the dispensing of active substances in any concentration over any time period as so determined by the operator of the device.

(C) Claim 28 recites a membrane "suitable" for supplying nutrient media. The metes and bounds of a "suitable" membrane for supplying nutrient media versus a membrane for supplying nutrient media cannot be determined.

(D) Claim 32 is vague and indefinite in the recitation of "semipermeable membrane" and "microporous membrane". Semipermeable and microporous are relative terms. Without a specific definition in the specification, the metes and bounds cannot be determined.

(E) Claim 39 is vague and indefinite in the recitation of "cell vitality". It is unclear if "cell vitality" refers to viability, growth, metabolism or all of the aforesaid. For purpose of examination, the term vitality will be read as viability, growth or metabolism.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over 103(a) Gruenberg (US 5,763,261) in view of Casciari et al (Journal of the National Cancer Institute, 1994, Vol. 86, pp. 1846-1852, reference of the IDS filed December 12, 2001).

Claim 25 is drawn to a device comprising an internal chamber, wherein a first supply device for introducing at least one nutrient medium and a second supply device for adding at least one gaseous medium are located in the interior chamber, wherein each supply device has a supply side an a removal side, and a cell culture space being formed between said supply devices and an inside wall of the interior chamber, and with the first supply device in a fluid connection with the supply side, connected to a nutrient medium dispensing unit including at least one nutrient medium container, and the second supply device connected in a fluid connection with the supply side connected to a gas metering unit including at least one gas supply container, wherein the cell culture space has a volume of at most 5 ml and at least 0.1 ml, and further wherein the device comprises an active substance supply container, and active substance dispensing unit, and a line system connecting the active substance supply container with the interior chamber for supplying at least one active substance to the cell culture chamber space, and wherein the active substance dispensing unit dispenses the active substances into the cell culture space according to an adjusted active substances concentration-time curve.

Claim 26 embodies the device of claim 25 wherein the first supply device includes a fluid connection on the removal side with a waste container. Claim 27 embodies the device of claim 25 wherein the first supply device includes a fluid connection on the removal side by a recirculation line comprising at least one nutrient medium container. Claim 28 embodies the device of claim 25 wherein the first supply device comprises at least one membrane suitable for supplying nutrient media. Claim 29 embodies the device of claim 25 wherein the second supply

device comprises at least one membrane suitable for gas exchange. Claim 30 embodies the method of claim 25 wherein the cell culture container comprises a bottom and a lid binding the interior chamber which are opposite to one another, and each comprising a transparent material. claim 31 embodies the device of claim 30 wherein the bottom of the cell culture container includes a heating system. Claim 32 embodies the device of claim 25 wherein the first supply device comprises at least one membrane that is a semipermeable membrane or a hydrophilic microporous membrane. Claim 33 embodies the device of claim 25 wherein the second supply device comprises at least one membrane that is an oxygenation membrane. Claim 34 embodies the device of claim 25 wherein the first and second supply devices comprise membranes that are hollow fibers. Claim 35 embodies the device of claim 34 wherein the hollow fibers are stacked in several layers in the interior chamber. Claim 36 embodies the device of claim 35 wherein the maximum distance between the hollow fibers forming each supply device is between 50 micrometers and 600 micrometers. Claim 37 embodies the device of claim 25 wherein the cell culture space comprises a volume of 0.3 ml to 3.0 ml. Claim 38 embodies the device of claim 25 wherein the supply device for adding the active substance comprises at least one active substance supply container, at least one active substance metering device and lines which connect the at least one active substance supply container through the at least one active substance metering device directly, or through the first supply device with the cell culture space of the cell culture container. Claim 39 embodies the device of claim 25 wherein the device further includes a monitor for cell vitality. Claim 40 embodies the device of claim 39 wherein the monitor for cell vitality comprises at least one sensor. Claim 41 embodies the device of claim 40 wherein the sensor comprises a fluorescent sensor. Claim 42 is drawn to a modular active substance testing system comprising at least two devices according to claim 25. Claim 43 embodies the modular active substance testing system of claim 42 comprising 6, 24 or 96 devices.

Greunberg teaches hollow fiber cartridges comprising a housing and a plurality of capillaries, and that the interior of the walls of the plurality of capillaries define a lumen extending between inflow and outflow openings , and the outside of the capillaries and the housing define an extra capillary space (ECS). , where cell growth or population expansion takes place. Greunberg teaches that the housing includes one or two ports providing access from the ECS so that cells may be added or removed therefrom (column 1, lines 8-25).

Greunberg teaches a device for the culturing of cells in bundles of hollow fibers, said device comprising an extracapillary connecting mechanism which includes a connecting chamber in fluid communication with the first and second primary orifices, a monitoring mechanism for monitoring the presence of oxygen gas and pH, a gas transfer mechanism for exchanging gas across a membrane separating the media from a controlled gaseous environment within the gas transfer mechanism, and a gas delivery mechanism for delivering specific gases such as oxygen, carbon dioxide and nitrogen to the controlled gaseous environment (column 5, lines 9-20). Gruenberg teaches that the monitoring mechanism for oxygen and pH combined with the controlled gas transfer mechanism provides a consistent homogeneous environment for the cells and overcomes the resistance of the capillaries to diffusion of oxygen because oxygen can be added to the inside of the ECS and does not have to diffuse from the lumen (column 7, lines 19-25).

Greunberg teaches that the device is automated by a computer-controlled mechanism capable of adjusting both the oxygen concentration, and pH and providing fresh growth media (column 9, lines 19-27, column 10, line 63 to column 11, line 13). Greunberg teaches an industrial scale device comprising a plurality of cartridges (column 11, lines 34-37). Greunberg teaches a gas flow metering device including a heating device (column 12, line 63 to column 13, line 13) and a growth media reservoir heated to 37 degrees (column 12, lines 18-23). The monitoring of pH by a pH electrode fulfills the specific embodiment of claim 39 and 40 drawn to a cell viability sensor, because monitoring the pH of a cell culture medium is indicative of monitoring cell growth in the culture. Because the claim drawn to monitoring cell "vitality" was rejected under 112, second paragraph, the teachings of Greunberg fulfill the specific embodiments of claims 39 and 40.

Greunberg teaches the above device further comprising an aphoresis instrument to harvest the cells by forcing the cells out by centrifugal force and capturing the flushing media into a waste container (column 15, lines 21-33).

Greunberg teaches that the cells which can be grown include mammalian cells including primary cells, transformed cells, neoplastic cells (column 16, lines 15-25).

Greunberg teaches all the embodiments of the instant claims with the exception of an active substance supply container, and active substance dispensing unit, and a line system

connecting the active substance supply container with the interior chamber for supplying at least one active substance to the cell culture chamber space, and wherein the active substance dispensing unit dispenses the active substances into the cell culture space according to an adjusted active substances concentration-time curve. Greunberg does not teach the specific limitation of claims 36 and 37 drawn to the device a maximum distance between the hollow fibers forming each supply device between 50 micrometers and 600 micrometers, and a cell culture space comprises a volume of 0.3 ml to 3.0 ml, respectively.

Casciari et al teach an improved method for screening anti-tumor drugs comprising exposing tumor cells cultured in hollow fibers to said drug. Casiciari et al teach hollow fibers with internal diameters between 450 micrometers and 600 micrometers (page 1847, second column, line 1), fulfilling the specific embodiments of claim 36. Casciari et al teach that hollow fibers comprising tumor cells were exposed to an anti-cancer drug in standard tissue culture well plates and then harvested for use in colorimetric dose-survival assays (page 1847, third column, line 27-37 under the heading "Drug Dose-Response Experiments"). Casciari et al teach that in general, differences in drug sensitivities between cells grown in monolayers and cells grown in hollow fibers are likely dues to limited diffusion of drug through the tumor mass and drug resistance related to microenvironmental or proliferate heterogeneity (page 1850-1851, bridging sentence). Casciari et al teach that the experiments with cells in monolayers do not provide information on how the chemotherapeutic response is affected by tumor heterogeneity in vivo or drug pharmokinetics (page 1846, second column lines 14-18). Casciari et al teaches that the cells were harvested from the hollow fibers after exposure to an anticancer drug and that cell viability was measured by means of staining with sulforhodamine B (page 1848, first column, under the heading of "Colorimetric Assays"). Casciari et al teach that hollow fiber tumors provide an advantage in vitro drug dose response studies because they form heterogeneous solid tumor masses which more closely mimic the tumor in situ than cells grown in monolayers (page 1847, first column, lines 28-33). Casciari et al teach that a limitation with using hollow fiber tumors is that there is a 3-4 day time window over which experiments can be performed at the maximum viable cell density, after which time the viable cell population begins to decline and that inappropriate timing could result in experiments being performed on dying cell populations. Casciari et al teach that another limitation is that the wall of the hollow fiber could potentially

slow down the mass transfer of rapidly used low molecular weight molecules such as oxygen and glucose from the surrounding medium to the tumor cells.

It would have been prima facie obvious to one of skill in the relevant art at the time the invention was made to attach an active substance supply container, and active substance dispensing unit, and a line system connecting the active substance supply container with the interior chamber of the ECH for supplying at least one anticancer drug or potential anticancer drug to the cell culture chamber space, and wherein the active substance dispensing unit dispenses the active substances into the cell culture space according to an adjusted active substances concentration-time curve which would dispense the anticancer drug or potential anticancer drug to hollow fiber tumors having the maximal viable cell density. One of skill in the art would be motivated to do so by the teachings of Casciari et al regarding the superiority of hollow fiber tumors over monolayer cell culture in the assessment of dose response on cancer cells, and the need for appropriate timing of the experiment to exposure hollow fiber tumors to the drug or potential drug at the time of maximal viable cell density. One of skill in the art would be motivated to screen a multiplicity of potential anticancer drugs or combinations of anticancer drugs on a multiplicity of tumors. The industrial sized device comprising a plurality of hollow fiber cartridges taught by Greunberg would allow for the exposure to different tumors to different potential anticancer agents or known anticancer agents or combinations thereof under computer control to allow for the treatment of the various hollow fiber tumors at maximum viable cell density. further, it would be obvious that the cells could be detached by the apheresis method taught by Greunberg and the staining with sulforhodamine B and detection of viable cells could be done by means of computer control, thus fulfilling the specific embodiment of claim 41 drawn to a fluorescent sensor. Neither Greunberg nor Casciari et al specifically teach the limitations of claim 37 requiring that the cell culture space comprises a volume of 0.3 ml to 3.0 ml. However, this is a common range for commercially available cell culture plates, and thus, one of skill in the art would be motivated to use similar volumes as used in monolayer cell culture. Neither Greunberg nor Casciari et al specifically teach the limitations of claim 30 requiring that the bottom of the cell culture space be a transparent material. However, it would be obvious to use a transparent plastic in order to be able to visually monitor the interior chamber.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 25-43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,410,307 in view of. Gruenberg (US 5,763,261) and Casciari et al (Journal of the National Cancer Institute, 1994, Vol. 86, pp. 1846-1852.

Greunberg teaches hollow fiber cartridges comprising a housing and a plurality of capillaries, and that the interior of the walls of the plurality of capillaries define a lumen extending between inflow and outflow openings , and the outside of the capillaries and the housing define an extracapillary space (ECS). , where cell growth or population expansion takes place. Greunberg teaches that the housing includes one or two ports providing access from the ECS so that cells may be added or removed therefrom (column 1, lines 8-25). Greunberg teaches a device for the culturing of cells in bundles of hollow fibers, said device comprising an extracapillary connecting mechanism which includes a connecting chamber in fluid communication with the first and second primary orifices, a monitoring mechanism for

monitoring the presence of oxygen gas and pH, a gas transfer mechanism for exchanging gas across a membrane separating the media from a controlled gaseous environment within the gas transfer mechanism, and a gas delivery mechanism for delivering specific gases such as oxygen, carbon dioxide and nitrogen to the controlled gaseous environment (column 5, lines 9-20). Gruenberg teaches that the monitoring mechanism for oxygen and pH combined with the controlled gas transfer mechanism provides a consistent homogeneous environment for the cells and overcomes the resistance of the capillaries to diffusion of oxygen because oxygen can be added to the inside of the ECS and does not have to diffuse from the lumen (column 7, lines 19-25).

Greunberg teaches that the device is automated by a computer-controlled mechanism capable of adjusting both the oxygen concentration, and pH and providing fresh growth media (column 9, lines 19-27, column 10, line 63 to column 11, line 13). Greunberg teaches an industrial scale device comprising a plurality of cartridges (column 11, lines 34-37). Greunberg teaches a gas flow metering device including a heating device (column 12, line 63 to column 13, line 13) and a growth media reservoir heated to 37 degrees (column 12, lines 18-23). The monitoring of pH by a pH electrode fulfills the specific embodiment of claim 39 and 40 drawn to a cell viability sensor, because monitoring the pH of a cell culture medium is indicative of monitoring cell growth in the culture. Because the claim drawn to monitoring cell "vitality" was rejected under 112, second paragraph, the teachings of Greunberg fulfill the specific embodiments of claims 39 and 40.

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Greunberg teaches that the cells which can be grown include mammalian cells including primary cells, transformed cells, neoplastic cells (column 16, lines 15-25).

Greunberg teaches all the embodiments of the instant claims with the exception of an active substance supply container, and active substance dispensing unit, and a line system connecting the active substance supply container with the interior chamber for supplying at least one active substance to the cell culture chamber space, and wherein the active substance dispensing unit dispenses the active substances into the cell culture space according to an

adjusted active substances concentration-time curve. Greunberg does not teach the specific limitation of claims 36 and 37 drawn to the device a maximum distance between the hollow fibers forming each supply device between 50 micrometers and 600 micrometers, and a cell culture space comprises a volume of 0.3 ml to 3.0 ml, respectively.

It would have been prima facie obvious to one of skill in the art at the time the invention was made to place hollow fibers for growing mammalian cells into the cell culture chamber of claims 7 and 8. One of skill in the art would have been motivated to do so by the teachings of Casciari et al on the advantages of hollow fiber tumor cells versus tumor cells grown in monolayers in the evaluation of anticancer drugs.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571)272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
Art Unit 1642

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER